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EXAMINER	
KOLKER, DANIEL E	
ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/764,068	HEN ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 Jan 2005, 25 Feb 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 28, 35, 42, 48, 55, and 62 - 92* is/are pending in the application.

4a) Of the above claim(s) *28,35,42,48,55,62-66,76 - 78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 67-75,79-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1, 28, 35, 42, 48, 55, and 62 – 92* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10 December 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments filed 18 January 2005 and 25 February 2005 have been entered. Claims 1, 28, 35, 42, 48, 55, and 62 – 92 are pending in the instant office action.

Election/Restrictions

2. Applicant's election of Group I in the reply filed on 18 January 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Newly submitted claims 76, 77, and 78 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the originally presented invention, the method of claim 1, does not require either the extraction of mRNA from brain tissue or the use of PCR; the method can be performed without either step. Claim 73, from which claims 76 – 78 depend, also does not require either mRNA extraction or PCR. These steps are explicitly required in claim 76; claims 77 and 78 depend from claim 76. Since the methods of claim 73 and claims 76 – 78 require different steps, they are considered by the examiner to be patentably distinct, as was indicated in the office action sent 13 December 2004.

3. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 76 – 78 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 28, 35, 42, 48, 55, and 62 – 66 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 18 January 2005.

Claims 1, 67 – 75, and 79 – 92 are under examination.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 67 – 75, and 79 – 91 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining whether fluoxetine, imipramine, desipramine, 8-OH-DPAT, or haloperidol (specification, p. 32 - 33), administered for a period of several days, two weeks, several weeks, or one month (specification p. 22 lines 29 – 31), or 5, 11, or 28 days (p. 39, line 28), increase the amount of bromodeoxyuridine (BrdU) incorporated into cells or Ki-67 mRNA in cells after a suitable period of time, wherein the period is 24 hours (p. 33, line 22), and wherein the cells are a subset of cells of any type that are dividing, does not reasonably provide enablement for administration of other compounds, for other non-specified amounts of time, use of agents other than BrdU or Ki-67 as markers of cell division, or other steps of determining if the agent increases cell division, or for determining if a specific type of cell is dividing, or waiting for other non-specified periods of time before animal sacrifice. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

The specification discloses the administration of fluoxetine, imipramine, desipramine, 8-OH-DPAT, or haloperidol to animals (p. 32 – 33). The specification contemplates that an agent can be essentially any molecule, without limitation, as described on p. 17. The claims list agents which are by function only: claim 80 is drawn to agents with no know function, claims 81 – 84 are drawn to compounds which are therapeutic for certain disorders, claims 85 – 87 are drawn to agents that interact with certain cellular components. Claims 88 – 91 are drawn to agents limited by their function, broad class, or site of interaction. None of claims 80 – 91 are limited structurally. While claim 92 recites specific agents, identified by structure in the specification, this claim depends from claim 1 which is rejected for not being fully enabled in scope, as detailed in the following paragraphs. Claim 92 is the only claim that recites specific structurally defined agents.

Claim 1 recites determining whether brain progenitor cell division is increased. Claim 67 recites "a compound which is a marker or cell division", however there is no structural limitation. The specification discloses methods based on the immunhistochemical recognition of BrdU, which is incorporated into the DNA of dividing cells, and the prior art clearly indicates that the Ki-67 protein is a marker of cell division (see, for example, Kee et al. 2002. J. Neurosci. Methods 115:97-105). However with the exception of claims 70 and 72 there is no requirement that a BrdU-based detection method be used. Claim 1 is sufficiently broad that it encompasses any method of determining, but the specification only provides working examples wherein BrdU is used as the method of determining whether changes in cell division have occurred.

The specification discloses, on p. 23, line 15 – p. 24 line 24, many mRNAs and hypothesizes that they could be used to detect brain progenitor cell division. However there are no working examples of any of these mRNAs being used as markers of brain progenitor cell division, and Gould et al. (2002; J Neurosci 22:619-623) teach that BrdU has particular advantages as a marker of cell division (p. 619, second column), which one would not expect of the vast number of mRNAs listed on p. 23 – 24 of the specification. BrdU is an analog of thymidine and is therefore incorporated into DNA when cells divide. Animals do not have endogenous BrdU, so any amount of this agent detected within cells is incorporated during division. That is not the case with the nucleic acids disclosed on pp. 23 – 24; all of them are expressed endogenously, and the extent to which they are expressed varies with cell type. A skilled artisan would have to resort to undue experimentation to use any substance other than BrdU, Ki-67, or ^{3}H-thymidine (a labeled nucleotide incorporated into dividing cells) as a marker of brain progenitor cell division, as neither the specification provides guidance as to how other agents are used as markers.

The claims are drawn to methods of determining whether brain progenitor cell division is increased. However, the guidance and working examples in the specification are not sufficient to allow a skilled artisan to conclude that any observed changes are actually in brain progenitor cells. The specification provides definitions for several terms (see pp. 17 – 21) but does not include a specific definition of the term "brain progenitor cell". The prior art teaching of Okano (2002. Keio J Med 51:115-128) indicates that both neural and glial progenitor cells exist (see Figure 1, p. 116); the term "brain progenitor cell" necessarily includes both, and can be construed to be so broad as to include any cell type that is a progenitor and is in the brain. For example, it includes those progenitors which give rise to blood vessels within the brain. The

specification discloses methods of determining whether an agent increases the amount of BrdU taken up by a cell. However, Kee et al. teach that BrdU is taken up by dividing cells (p. 97, second column). The scope of dividing cells is considerably larger than progenitor cells, as progenitor cells by definition are those that give rise to additional cell types (i.e. as explained on p. 116 of Okano, neural progenitor cells give rise to multiple types of neurons, and glial progenitor cells give rise to astrocytes and oligodendrocytes), but there are of course cells that divide and are not progenitor cells, including tumors, for example. Methods that use BrdU are not specific for progenitor cells. Similarly, Ki-67 is expressed in all cells undergoing mitosis (Scholzen et al. 2000. J Cell Physiol 182:311-322; see p. 312, second column) and is not specific to progenitor cells.

Claims 67 and 73 are drawn to suitable durations of time. Claims 69 limits one of the durations to 2 – 24 hours. The specification gives specific examples of time periods of administration of the agent: several days, two weeks, several weeks, or one month (specification p. 22 lines 29 – 31), or 5, 11, or 28 days (p. 39, line 28). The specification also indicates that the period between administration of BrdU and sacrifice can be 24 hours (p. 33, line 22). However, different agents and different methods of measuring brain progenitor cell division would require different lengths of time. For example, Lai et al. (2003. Nature Neuroscience 6:21 – 27) teach that brain progenitor cell division increases when rats are administered a single dose of virus carrying cDNA that encodes sonic hedgehog, if the period between injection and BrdU injection is 2 weeks (p. 26, second column). However Zhang et al. (2002. Stroke 33:2675-2680) teach that sildenafil induces brain progenitor cell division when given for seven consecutive days, and BrdU is given for 14 consecutive days (abstract, and p. 2676, Bromodeoxyurdine Labeling). The kinetics of agent incorporation (for BrdU) and production (for Ki-67) also differ. Kee et al. (2002) teach that BrdU's incorporation varies across species, and it is only taken up during the S phase of cell division. On the other hand, Ki-67 is expressed in all species examined so far, and is produced during all phases except G_0 (see Table 1, p. 104). Ki-67 is produced within the cell and therefore can be detected immunologically as soon as the protein is made, but BrdU incorporation is dependent upon dose, blood flow, metabolism, and cell cycle phase (see Gould et al. p. 620, first column). The specification does not give specific guidance to a skilled artisan in selecting a time period which is suitable for either the interval between administration of the agent and the marker of brain progenitor cell division or the interval between administration of the marker and sacrifice, even

though the durations of these intervals depend on the agent and marker being used. There is not even guidance as to how one should determine what time periods are suitable. Therefore a skilled artisan would be forced to resort to undue experimentation in order to practice the claimed methods commensurate in scope with the claims.

The claims are drawn to methods of determining whether brain progenitor cell division is increased. Claim 73, part (c) for example, is drawn to determining the amount of protein and/or nucleic acid that is indicative of brain cell division, but the proteins or nucleic acids to be determined are not named. It is not apparent whether these unnamed proteins and nucleic acids are present in all brain progenitor cells, including glial progenitor cells, blood-brain-barrier cells, and neural stem cells. Therefore a skilled artisan would have to resort to undue experimentation to practice the claimed methods. The artisan would have to first identify brain progenitor cells, then determine which compounds are markers of cell division as recited in claim 67, determine the suitable amounts of time, and determine which nucleic acids and/or proteins are indicative of brain progenitor cell division, as recited in claim 73. Only after doing a large amount of experimentation would a skilled artisan be able to practice the methods commensurate in scope with the claims.

The nature of the invention, labeling of dividing brain progenitor cells, is complex. Gould et al. teach that methodological problems exist in BrdU-based methods of detection, (see p. 619 – 622) including the recent findings that BrdU does not label all dividing cells, and that low doses of BrdU do effectively label all brain regions. The specification gives only limited working examples, as detailed above, and provides little guidance as to how to determine, for example, which agents should be used, at what doses, what periods of time should be chosen, and how those should be selected. The claims are broad because they are not limited by specific combinations of methodologies and steps (i.e. time period, agent administered, and marker chosen). Therefore it would require undue experimentation on the part of a skilled artisan in order to be able to practice the claimed methods commensurate in scope with the claims.

6. Claims 1, 67 – 75, and 79 – 91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 1 is drawn to a method of determining whether an agent increases brain progenitor cell division. Dependent claims are drawn to methods of determining whether agents that can treat certain diseases or conditions, or those with no known function, increase brain progenitor cell division. The specification provides no guidance or structural limitations on any of the disease-related categories (i.e. drugs that are known therapeutics of cognitive or non-mental disorders). The only exceptions are the chemicals Hh-Ag 1.1, Hh-Ag 1.2, Hh-Ag 1.3, and certain derivatives (defined on pp. 20 – 21). The specification (p. 17, lines 19 – 21) defines agents to include, "without limitation, an organic compound, a nucleic acid, a polypeptide, a lipid, and a carbohydrate". The claims are drawn to broad genera and subgenera of chemicals for which no structure is provided. For example, claim 80 is drawn to an agent that has no known function, and claim 81 is drawn to an agent is a known therapeutic for a cognitive disorder. Claim 86 is drawn to agents that are known to inhibit any cellular pathway that is associated with cell division, although it is unclear what these pathways are, or what the chemical structures of said agents are. The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of agents, or all the methods of determining that are encompassed by the claims. Therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation of an agent, or of methods of determining. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Therefore the written description requirement has not been met.

While the specification discloses that BrdU can be used as an agent that is incorporated during cell division, claim 1 is drawn to determining whether brain progenitor cell division increases. The term "brain progenitor cell" is not explicitly defined in the specification, and methods of determining if the entire genus of brain progenitor cell division is increased has not been described by applicant. This is a broad genus that includes, at the minimum, neural and glial progenitor cells, and could reasonably include any progenitor cell (i.e. blood vessel progenitor cells) that are in the brain and tumor progenitors.

The specification has not described the entire genus of "determining" steps, although certain subgenera (i.e. *specific* instantiations of BrdU-based methods) have been described. Similarly, claim 67, part b, recites administering "a compound which is a marker of cell division",

but the specification has not described the full genus of said compounds. Claim 73, part c, is drawn to determining the amount of protein and/or nucleic acid that is indicative of brain progenitor cell division. However, the protein and/or nucleic acid is not enumerated. In order to practice the method, the skilled artisan would have to use either an antibody (for protein-based methods) or a nucleic acid probe (for nucleic acid-based methods) but neither is described. Finally, the claims, with the exception of claim 69, do not recite any time periods involved, even though the claims either explicitly (claims 67 and 73) or implicitly recite suitable time periods.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 86 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim is drawn to methods of determining whether agents increase brain progenitor cell division, wherein the agents are known to be inhibitors of pathways whose inhibition is associated with cell division. This language is confusing, as it is unclear whether applicant is referring to pathways that inhibit cell division, or pathways that are "associated with" cell division. The term "associated with" can reasonably be construed to mean either increasing or decreasing. It is unclear whether the agent is one that will increase cell division (as would be expected for inhibiting a pathway that inhibits cell division) or decrease cell division (as would be expected for inhibiting a pathway that stimulates cell division).

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Priority Determination

10. 35 U.S.C. § 119(e) states that:

> An application for patent filed under section 111(a) or section 363 of this title for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in a provisional application filed under section 111(b) of this title, by an inventor or inventors named in the provisional application, shall have the same effect, as to such invention, as though filed on the date of the provisional application filed under section 111(b) of this title, if the application for patent filed under section 111(a) or section 363 of this title is filed not later than 12 months after the date on which the provisional application was filed and if it contains or is amended to contain a specific reference to the provisional application.

11. Applicant is advised that the instant application can only receive benefit under 35 U.S.C. § 119(e) from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, with respect to the now claimed invention. Because support for claims 88, insofar as it refers to agents that upregulate the sonic hedgehog pathway, and 89 – 92 is provided in provisional application 60/526190 (filed 1 December 2003) but not in provisional application 60/442081 (filed 23 January 2003), the examiner has determined that the effective filing date for those claims is 1 December 2003. Applicant clearly had not conceived of the use of any agonists of the sonic hedgehog pathway in methods to detect brain progenitor cell division in application 60/442081.

12. Claims 1, 67 – 75, 79, 85, and 87 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoshimura et al. (2001. Proc Natl Acad Sci USA 98:5874-5879, reference 87 on the information disclosure statement filed 10 December 2004). The claims are drawn to methods of determining whether a compound increases the rate of brain progenitor cell division in an animal. This general method is well-known in the art and can be practiced by administering, for example, bromodeoxyuridine (BrdU) or ^{3}H-thymidine to an animal, both of which are markers of cell division. Yoshimura et al. disclose the results of experiments in which they administered kainate to mice, followed by BrdU. They then counted the number of BrdU labeled cells, thereby determining whether the agent (kainite) increased brain progenitor cell division, meeting the limitations of claim 1. Yoshimura et al. administered the agent (kainite) for a suitable amount of time, administered BrdU, sacrificed the animals after a suitable amount of time, counted the labeled cells (see p. 5875, first sentence of Results), and compared the results to control animals see Figures 2 and 3, for example), thereby meeting the limitations of claim 67. Mice were used, meeting the limitations of claims 68 and 74, some being killed 24 hours after the final BrdU injection, meeting the limitations of claim 69. BrdU was the marker of brain progenitor cell division, meeting the limitation of claim 70. The hippocampus was examined, meeting the limitations of claims 71 and 75 (see Figures 1 – 3). The animals were killed by transcardial perfusion (see p. 5875, second complete paragraph), brain tissue was sectioned, labeled with anti-BrdU antibody, and cells were counted (see p. 5875, first paragraph

of second column), meeting the limitations of claim 72. Because BrdU is incorporated into nucleic acid, and Yoshimura et al. counted the number of cells that were stained positive in an immunohistochemical assay performed ex vivo, the teachings also meet the limitations of claim 73 and 79. Some animals received FGF-2 in the form of gene therapy; since FGF-2 stimulates cell division and activates its own receptor, this meets the limitations of claims 85 and 87.

13. Claims 1, 67, 68, 70 – 75, 79, 81 – 83, and 88 are rejected under 35 U.S.C. 102(b) as being anticipated by Malberg et al. (2000. J Neurosci 20:9104 – 9110, reference 53 on the information disclosure statement filed 10 December 2004), as evidenced by Physician's Desk Reference. The claims are drawn to methods of determining whether an agent induces brain progenitor cell divsion. Claims 81 – 83 and 88 further limit the agent. Malberg et al. teach a method of determining whether an agent increases brain progenitor cell division, wherein the agent is either fluoxetine or haloperidol (see p. 9104, last full paragraph), meeting the limitations of claim 1. The agents were administered for a suitable amount of time (21 days for fluoxetine and 1 – 28 days for haloperidol, see p. 9104, last full paragraph), BrdU was administered, (see paragraph spanning pp. 9104 – 9105), animals were sacrificed, cells labeled with BrdU were counted and compared to controls (see paragraph spanning pp. 9104 – 9105, as well as Figures 3 and 4), thereby meeting the limitations of claim 67. Rats were used, meeting the limitation of claims 68 and 74. BrdU was used as the marker of cell division, meeting the limitation of claim 70. The hippocampus was examined, meeting the limitations of claims 71 and 75 (see Fgure 2). The animals were killed by transcardial perfusion (see paragraph spanning pp. 9104 – 9105), brain tissue was sectioned, labeled with anti-BrdU antibody, and cells were counted (see p. 9105, first column, under Immunohistochemistry), meeting the limitations of claim 72. Because BrdU is incorporated into nucleic acid, and Malberg et al. counted the number of cells that were stained positive in an immunohistochemical assay performed *ex vivo*, the teachings also meet the limitations of claim 73 and 79. Malberg et al. teach the administration of both fluoxetine (see p. 9104, last full paragraph), which is a selective serotonin re-uptake inhibitor known to be effective for treating depression (p. 9105, second column second paragraph under RESULTS), and haloperidol (see p. 9104, last full paragraph), thereby meeting the limitations of claims 81, 82, and 88. Haloperidol is well-known to be effective in the treatment of schizophrenia (see Physician's Desk Reference entry for Haldol, particularly the section "Indications and Usage", p. 2), therefore the teachings of Malberg et al. meet the limitations of claim 83.

14. Claims 1, 67, 68, 70, 71, 73 – 75, 79, 84, 87, and 88 are rejected under 35 U.S.C. 102(a) as being anticipated by Zhang et al. (2002. Stroke 33:2675-2680). The claims are drawn to methods of determining whether an agent induces brain progenitor cell divsion. Dependent claims are further limited to rats (claims 68 and 74), hippocampal or subventricular tissue (claims 71 and 75), the use of BrdU (claim 70), wherein the agent is a known therapeutic for a non-mental disorder (claim 84), is known to affect an enzyme (claim 87) and is selected from a group including phosphodiesterase inhibitors (claim 88). Zhang et al. teach a method of determining whether sildenafil increases brain progenitor cell division by administering it to animals and determining whether the agent increases brain progenitor cell division, meeting the limitation of claim 1. Zhang et al. administered their agent for a suitable duration (6 days, see p. 2675, Experimental Protocols), administered BrdU as the marker of cell division (p. 2676, end of first column), sacrificed the animals after a suitable period of time (14 days after the last BrdU injection, see p. 2676, end of first column) quantitated the number of labeled cells (see p. 2676, second column, Image Analysis and Quantification), and compared the results to controls (see p. 2677, Table 1), meeting the limitations of claim 67. The experiments were done on rats, meeting the limitations of claims 68 and 74. BrdU was the marker of cell division, meeting the limitation of claim 70. The tissue examined was hippocampal (specifically dentate gyrus and subvetricular zone, see p. 2676, second column, Image Analysis and Quantification), meeting the limitations of claims 71 and 75. The agent was given for a suitable duration (6 days, see p. 2675, Experimental Protocols), animals were sacrificed, the amount of nucleic acid indicative of cell division (i.e. marked by anti-BrdU staining) was determined, and compared to controls (see p. 2676, Immunohistochemistry and Image Analysis and Quantification), meeting the limitations of claim 73. The method used was immunohistochemistry, meeting the limitation of claim 79. Sildenafil is known to be a phosphodiesterase inhibitor which is a therapeutic compound for treating impotence, thereby meeting the limitations of claims 84, 87, and 88.

15. Claims 1, 67, 68, 70 – 75, 79, 85, and 87 – 91 are rejected under 35 U.S.C. 102(b) as being anticipated by Lai et al. (Proceedings of the Second Joint EMBS/BMES Conference. October 23 – 26, 2002, p. 743 – 744), as evidenced by Frank-Kamenetsky et al. (reference 28 on the information disclosure statement filed 10 December 2004). The claims are drawn to methods of determining whether an agent increases brain progenitor cell division. Claims 85 – 91 are further limited to agents that are known to stimulate a cellular pathway whose stimulation is associated with an increase in cell division (claim 85), wherein the agent in known to bind to

or otherwise affect a known target (claim 87), wherein the agent upregulates the sonic hedgehog (Shh) pathway (claims 88 and 89), antagonizes Patched (claim 90), or is an agonist of Smoothened (claim 91). Lai et al. teach methods of determining whether an agent increases neurogenesis in rats using BrdU (see p. 744, first column, last paragraph). Lai et al. teach methods of determining if an agent increases brain progenitor cell division by injecting BrdU (p. 744, first column), to rats (p. 744, "Animal surgeries"), wherein the agent is a viral vector comprising sonic hedgehog cDNA, thereby meeting the limitations of claim 1. Lai et al. administered the agent for a suitable duration (once, p. 744 under Animal Surgeries), administered BrdU which is a marker of cell division (Animal Surgeries), sacrificed the animals after a suitable period (8 days, Animal Surgeries), the number of cells taking up the label were quantitatively determined (see paragraph spanning the columns on p. 744), and comparing to controls (p. 744, second column, lines 1 – 2), meeting the limitations of claim 67. Rats were used, meeting the limitations of claims 68 and 74. BrdU was used, meeting the limitation of claim 70. The hippocampus was the tissue of interest, meeting the limitations of claims 71 and 75. Animals were perfused and the brain was sectioned (p. 744, Animal Surgeries), the tissue was labeled with an anti-BrdU antibody (p. 743 final paragraph), and the labeled cells were counted (see sentence spanning the two columns of p. 744), meeting the limitations of claim 72. Lai et al. administered the agent for a suitable duration (once, p. 744 under Animal Surgeries), sacrificed the animals after a suitable duration, nucleic acid indicative of brain progenitor cell division (i.e. stained by BrdU immunohistochemistry) was determined ex vivo, and compated to controls (those that did not receive the cDNA), meeting the limitations of claim 73. Immuno-histochemistry was used as the method, meeting the limitation of claim 79. The cDNA administered encoded sonic hedgehog, which is a stimulator of the sonic hedgehog pathway, known to be associated with an increase in cell division, thereby meeting the limitations of claims 85 and 89. Sonic hedgehog binds to its own receptor, meeting the limitation of claim 87.

The sonic hedgehog pathway has been well-described. For example, Figure 4 of the prior art teaching of Frank-Kamenetsky et al. indicates that Hedgehog inhibits the activity of Patched, and that Patched inhibits the activity of Smoothened. Therefore an agonist of the Hedgehog pathway (e.g. a virus containing the cDNA that encodes Shh) inherently inhibits Patched and inherently activates Smoothened (i.e. by inhibiting the inhibition). Therefore the teachings of Lai et al. meet the limitations of claims 90 and 91.

16. Claims 1, 67 - 75, 79, and 85 – 91 are rejected under 35 U.S.C. 102(a) as being anticipated by Lai et al. (2003, Nature Neuroscience 6:21 – 27, reference 49 on the information disclosure statement filed 10 December 2004, published online 2 December 2002). Lai et al. teach methods of determining if agents increase brain progenitor cell division, wherein the agents are either cDNA encoding Shh or cyclodextrin. Lai et al. teach administering the agent for a suitable amount of time (once for the cDNA and cyclodextrin), administering BrdU as a marker of cell division, sacrificing the animals after a suitable period of time (one day or three weeks after the final injection, see p. 26 second column), quantitated and compared to controls (see p. 24, Figure 4), meeting the limitations of claim 67. Rats were used, meeting the limitations of claims 68 and 74. Some animals were killed within 24 hours ("the next day", p. 26 second column) after the final BrdU injection, meeting the limitation of claim 69. BrdU was used, meeting the limitation of claim 70. Hippocampal tissue was used, meeting the limitations of claims 71 and 75 (see Figure 4, for example). Brains were perfused, tissues were sectioned and stained with anti-BrdU, and counted (see p. 26, second column), meeting the limitations of claim 72. The agents were administered for, and animals were sacrificed after, suitable durations (as detailed earlier in this paragraph), and the amount of nucleic acid indicative of brain progenitor cell division (i.e. stained in the BrdU immunohistochemistry method) was determined ex vivo, and compared to controls that did not receive the cDNA, meeting the limitations of claim 73. An immunhistochemistry method was used, meeting the limitation of claim 79. cDNA encoding Shh was administered, and as detailed in the previous paragraph this binds to its own receptor and is known to stimulate a pathway associated with cell division, meeting the limitations of claims 85 and 87. Cyclodextrin was also administered which is an inhibitor of Shh (see p. 23, second column, "Inhibition of Shh"). Shh is a pathway that is associated with cell division, as taught by Lai et al. and numerous others (see the second paragraph of p. 21, and references 17 – 22 cited therein). Therefore the administration of cyclodextrin as taught by Lai et al. meets the limitations of claim 86. The cDNA upregulates the sonic hedgehog pathway, meeting the limitations of claims 88 and 89. Agonists of the Hedgehog pathway (e.g. a virus containing the cDNA that encodes Shh) inherently inhibit Patched and inherently activate Smoothened (i.e. by inhibiting the inhibition). Therefore the teachings of Lai et al. meet the limitations of claims 90 and 91.

17. Claims 1, 67 – 70, 73 – 74, 79, 86, 87, and 90 are rejected under 35 U.S.C. 102(b) as being anticipated by Wallace (1999. Current Biology 9:445-448).

Wallace teaches methods of detemining if compounds increase brain progenitor cell division. Wallace teaches administering agents, specifically hybridomas that secrete anti-Shh antibodies into the brains of mice (p. 445, final paragraph) for a suitable amount of time (hybridomas were implanted until animals were sacrificed), administering a marker of cell division (BrdU, p. 446, second column), sacrificing the animals after a suitable period of time (2 hours after the final injection of BrdU, p. 446 second column), quantitatively determining the amount of BrdU incorporated in the brain tissue (p. 447, end of legend for Figure 3), and comparing to controls (implanted with other hybridomas, see sentence spanning p. 446 – 447), meeting the limitations of claims 1 and 67. Mice were used, meeting the limitation of claims 68 and 74. The period of time between the last injection of BrdU and sacrifice was 2 hours, meeting the limitation of claim 69. BrdU was used, meeting the limitation of claim 70. The agent was administered for a suitable period of time, animals were sacrificed after a suitable period of time, the amount of nucleic acid with BrdU (i.e. indicative of brain progenitor cell division) was determined ex vivo, and compared to controls, meeting the limitations of claim 73. Immunohistochemistry was used (see legend for Figure 3), meeting the limitation of claim 79. The agent, anti-Shh antibodies, bind to Shh, which is a molecular target, meeting the limitation of claim 87. The agent also inhibits the Shh pathway, by binding to Shh, and inhibition of this pathway is associated with cell division, specifically a decrease in cell division (see p. 447 lines 1 – 3); therefore the teachings also meet the limitations of claim 86. As set forth above, Patched is the receptor for Shh, and since the antibodies bind Shh they prevent it from binding Patched. Therefore the agent is inherently an antagonist of Patched. Even though it does not bind to Patched it decreases the activity of Patched, so it is an antagonist, and meets the limitation of claim 90.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 1, 67, 80, 85, and 87 – 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frank-Kamenetsky et al., in view of Wallace (1999). Frank-Kamenetsky et al.

teach screening 140,000 compounds that were generated by combinatorial chemistry, and did not have known therapeutic uses (thereby meeting the limitation of claim 80), in a cell-based assay (see pp. 10.3, Results section and 10.16, Chemical libraries section). Frank-Kamenetsky et al. disclose the structure of Hh-Ag 1.1, Hh-Ag 1.2, and Hh-Ag 1.3 (see page 10.4, Figure 1), meeting the limitations of claim 92. Frank-Kamentsky et al. further teach that Hh-Ag 1.1 activates the sonic hedgehog pathway *in vivo* (see p. 10.6, second column), meeting the limitations of claims 88 and 89, and binds to a known target (see p. 10.12, end of first complete paragraph), meeting the limitations of claim 87. As set forth previously, stimulation of the Shh pathway is known to be associated with an increase in cell division, meeting the limitations of claim 1. Frank-Kamenetsky et al. teach that hedgehog destabilizes Patched (p. 10.9), meeting the limitations of claim 90, and that Hh-Ag 1.1 is an agonist of Smoothened (p. 10.10, first paragraph), meeting the limitations of claim 91. Finally, Frank-Kamentsky et al. teach a method of determining whether said compound induces proliferation of neuronal precursor cells *in vitro* (see p. 10.3, In vitro assay of neuronal precursors) and explicitly contemplate the administration of Hh-Ag 1.1 as a therapeutic agent (see particularly p. 10.16, second column "Therapeutic potential of a Hh-pathway agonist"). Frank-Kamentsky et al. do not teach a method of determining whether an Hh-Ag 1.1 or any agonist of the sonic hedgehog pathway increases neurogenesis *in vivo*.

Wallace teaches administration of agents and determination of whether said agents increase brain progenitor cell division in vivo, including hybridomas that secrete anti-Shh antibodies (p. 445, final paragraph). Wallace also teaches administering agents for a suitable duration of time, administering BrdU, sacrificing the animal after a suitable period of time, quantitatively determining the amount of BrdU incorporation in the brain, and comparing to controls. It would have been obvious to one of ordinary skill in the art to test the compound identified by Frank-Kamenetsky et al. in the assay described by Wallace with a reasonable expectation of success. A motivation for doing so would be to determine if in fact Hh-Ag 1.1 was able to induce neurogenesis *in vivo*, as it had been shown capable of doing so *in vitro*, and Frank-Kamentsky et al. clearly contemplated the use of Hh-Ag 1.1 as a therapeutic in neurodegenerative diseases.

20. Claims 1, 67, and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujii (1997. Cancer Causes and Control 8:524 – 528) in view of Yoshimura et al. Fujii teaches the administration of nimustine to pregnant rats and determining that the offspring had a

decrease in the frequency of kainic acid-induced wet dog shakes (see p. 526, second column, and p. 527, both columns). Fujii further teaches that nimustine is an anti-cancer agent (p. 526 second column), and hypothesizes that the effects of prenatal exposure to nimustine are mediated by alterations in neurogenesis (see p. 527, paragraph that spans the two columns). Fujii does not teach a method of determining if an agent increases brain progenitor cell division.

As detailed above in the rejections under 35 USC 102, Yoshimura et al. teach a method of determining whether an agent increases brain progenitor cell division. It would have been obvious to one of ordinary skill in the art to determine if nimustine modulates brain progenitor cell division in prenatally exposed rats, by using the agent from Fujii et al. in the method of Yoshimura et al. with a reasonable expectation of success, given the art-accepted means for measuring brain progenitor cell division. A motivation for doing so would be to determine if the effects observed by Fujii are in fact due to alterations in neurogenesis, as hypothesized.

Conclusion

21. No claim is allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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April 6, 2005

SHARON TURNER, PH.D.
PRIMARY EXAMINER
4-11-05